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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,605	LECHLER ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-9,12-15,24,25,27 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-9,12-15,24,25,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/19/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Sections of Title 35, U.S. Code not found in this action can be found in a previous action.

Claims 2, 5, 9, 12, 27 and 28 have been amended. Claims 1, 2, 5-9, 12-15 , 24, 25, 27 and 28 are pending and under consideration.

Applicant acknowledges the withdrawing of the restriction requirement and request that another restriction requirement or an election of species be set forth. It is noted that the examiner never had any intention of issuing a modified restriction requirement or election of species requirement and that it would not be appropriate to do so after the first action on the merits.

Claims 1, 2, 6-9, 13-15, 24, 25, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Etlinger (EP 429,816) in view of Maher et al (Journal of Immunology, 1996, vol. 11, pp. 3838-3844, reference of the IDS filed June 19, 2001), Van Gool et al (Res Immunology, Vol. 146, pp. 183-196) and Mueller et al (WO 97/11971, reference of the IDS filed June 19, 2001).

Claim 1 is drawn to a method of improving tolerance to a xenograft comprising immunizing an animal with an immunogen comprising at least one T-cell epitope and at least one porcine B-cell epitope, wherein said B-cell epitope is capable of mediating rejection of said xenograft, Claim 2 embodies the method of claim1 wherein said B-cell epitope is a peptide comprising at least 9 contiguous amino acids of a porcine

Claims 24 and 25 embody the methods of claims 1 and 7, respectively wherein said B-cell epitope has less than 75% sequence identity to a corresponding region of an equivalent human polypeptide

Etlinger teaches a method for inducing a humoral response comprising the administration of an antigen which comprises a B-cell epitope linked to a carrier protein, wherein said carrier protein comprises a T-cell helper epitope devoid of T suppressor function (page 2, lines 17-25 and page 4, lines 14-28 and page 4, line 49 to page 5, line 9) fulfilling the specific embodiment of claim 15, drawn to a carrier. Etlinger teaches examples of carrier proteins as de-toxified tetanus toxin or diphtheria toxin, thus fulfilling the specific embodiment of claims 6 and 14

drawn to a tetanus toxoid (page 2, lines 27-30). Etlinger teaches that the B-cell epitopes are capable of inducing the formation of antibodies which bind to the native molecule in a host (page 2, lines 18-22). Etlinger teaches that in general B-cell epitopes comprise at least 6 amigo acids and that larger fragments may represent more than one epitope or overlapping epitopes (page 6, lines 37-42). Etlinger does not teach a vaccine comprising a B cell epitope of porcine CD86 linked to tetanus toxoid, nor a method for improving tolerance to a xenograft.

Maher et al teach that porcine endothelial CD86 is a major co-stimulator of xenogenic human T-cells (title) fulfilling the specific embodiment of a porcine polypeptide expressed by vascular endothelial cells of a xenograft. Maher et al teach that in the case of transplanted vascularized solid organs, graft endothelial cells may serve both as targets and as the Ag-presenting cells that initiate host-antigraft responses (page 3838, first column , last sentence). Maher et al teach that porcine endothelial cells interact with human T-cell CD28 providing a co-stimulatory response that could be blocked by anti-CD28 antibodies or CTLA-Ig fusion proteins (page 3838, second column, lines 14-16). It is known in the art that CD86 is synonymous with B7.2, and that B7.2 interacts with the T-cell receptor at CD28.

VanGool et al teach that CD86 may provide the critical co-stimulatory signal involved i the decision between immunity and anergy (page 189, first column, lines 10-12 under the heading "The relative roles of CD80 and CD86 as co-stimulatory molecules"). VanGool et al teach that immunosuppression and anergy is induced by CD80/CD86-blocking agents in combination with CsA and that this combination should be explored to establish the most efficacious treatment regiment for the prevention of graft rejection and GVHD (page 190, first column, lines 34-40)

Mueller et al teach the treatment of patients suffering from xenotransplant rejection comprising the administration of porcine cell interaction protein antibodies (page 23, lines 6-11). Mueller et al teach that therapeutic agents for use in the prevention and treatment of porcine xenograft reaction include antibodies that bind to porcine CD86 but not to human CD86 which fulfills the specific embodiments of claims 24 and 25. Mueller et al teach that the term "antibodies" refers to immunoglobulins produced in vivo as well as those produced in vitro (page 26, lines 13-15).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to administer an antigen comprising a B-cell epitope of the extracellular domain of porcine CD86 and a T-helper cell epitope of tetanus toxoid to an individual receiving a porcine vascularized organ. One of skill in the art would have been motivated to do so by the teachings of Maher et al regarding the ability of CD86 on porcine endothelial cells to activate human T-cells, the teachings of Maher et al that blocking of said interaction by the administration of anti-CD28 antibodies and prevent stimulation of the human T-cells; the teachings of Mueller et al on the therapeutic effect of anti-CD86 antibodies in an individual suffering from porcine xenograft rejection and the contemplation of Mueller et al that said antibodies can be also immunoglobulins generated in vivo. As stated above, it flows logically from this that blocking of the CD86 CD28 interaction with anti-CD86 antibodies would also prevent the stimulation of t-cells. Further, the teachings of vanGool identify the CD86 receptor as the critical co-stimulatory ligand involved in the decision between immunity and anergy in a T-cell. and the teachings of vanGool that CD80/CD86-blocking agents can synergize with CsA for complete immunosuppression and that this would suggest that the synergist combination be used to establish an efficacious treatment regimen for the prevention of graft rejection and GVHD would motivate one of skill in the art to choose a B-cell epitope from the extracellular domain of porcine CD86 because of the teachings of Maher et al which indicate that the graft endothelial cells are serving as antigen -presenting cells. One of skill in the art would realize that only the extracellular domain of CD86 would be accessible for interaction with human T-cells and thus, antibodies which would bind to the intracellular domain would interfere with the activation of human T-cells. It would be further obvious that the administration of at least 9 amino acids of CD86 would guarantee that at least one B cell epitope was present in the antigen, as Etlinger teaches that an antigenic determinant comprises at least 6 ammo acids.

Claims 1, 6-8, 14, 15, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Etlinger (EP 429,816) in view of Maher et al (Journal of Immunology, 1996, vol. 11, pp. 3838-3844, reference of the IDS filed June 19, 2001), Van Gool et al (Res Immunology, Vol. 146, pp. 183-196) and Mueller et al (WO 97/11971, reference of the IDS filed June 19, 2001).

Etlinger teaches a method for inducing a humoral response comprising the administration of an antigen which comprises a B-cell epitope linked to a carrier protein, wherein said carrier protein comprises a T-cell helper epitope devoid of T suppressor function (page 2, lines 17-25 and page 4, lines 14-28 and page 4, line 49 to page 5, line 9) fulfilling the specific embodiment of claim 15, drawn to a carrier. Etlinger teaches examples of carrier proteins as de-toxified tetanus toxin or diphtheria toxin, thus fulfilling the specific embodiment of claims 6 and 14 drawn to a tetanus toxoid (page 2, lines 27-30). Etlinger teaches that the B-cell epitopes are capable of inducing the formation of antibodies which bind to the native molecule in a host (page 2, lines 18-22). Etlinger teaches that in general B-cell epitopes comprise at least 6 amigo acids and that larger fragments may represent more than one epitope or overlapping epitopes (page 6, lines 37-42). Etlinger does not teach a vaccine comprising a B cell epitope of porcine CD86 linked to tetanus toxoid, nor a method for improving tolerance to a xenograft.

Mueller et al teach the treatment of patients suffering from xenotransplant rejection comprising the administration of porcine cell interaction protein antibodies (page 23, lines 6-11). Mueller et al teach that therapeutic agents for use in the prevention and treatment of porcine xenograft reaction include P-selecting antibodies that bind to porcine P-selectin but not to human p-selectin and antibodies which bind to porcine VCAM but not to human VCAM (page 8, lines 4-13). Both of VCAM and p-selecting are expressed by porcine vascular endothelial cells (page 4, line 18 and page 6, line 27), thus fulfilling the specific embodiment of claim 8.. Mueller et al teach that the term "antibodies" refers to immunoglobulins produced in vivo as well as those produced in vitro (page 26, lines 13-15).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to administer an antigen comprising a B-cell epitope from porcine p-selectin and a T-helper cell epitope of tetanus toxoid or a B-cell epitope of porcine VCAM and a T-helper cell epitope of tetanus toxoid to an individual receiving a porcine vascularized organ. One of skill in the art would have been motivated to do so by the teachings of Mueller et al on the therapeutic effect of anti-porcine p-selectin antibodies or anti-porcine VCAM antibodies in an individual suffering from porcine xenograft rejection and the contemplation of Mueller et al that said antibodies can be also immunoglobulins generated in vivo. It would be further obvious that the administration of at least 9 amino acids of porcine p-selectin or porcine VCAM would guarantee

that at least one B cell epitope was present in the antigen, as Etlinger teaches that an antigenic determinant comprises at least 6 ammo acids and the resulting B-cell epitopes would have less than 75% sequence identity by virtue of the fact that they elicit immunoglobulins that bind to porcine p-selectin or porcine VCAM rather than human p-selectin or human VCAM..

Applicant argues that the examiners reasoning is fatally flawed in the combination of the references because there is no reasonable expectation that would flow from the blocking of the CD28 interaction by an antibody which binds to CD28 and the blocking of the CD86 interaction with an antibody that bind to CD86. This has been considered but not found persuasive. Mueller et al teaches a method of treating individuals for xenograft rejection comprising administering an antibody which binds to porcine CD86 but not to human CD86. Thus, it would be reasonable to expect that the CD86 co-stimulatory signal can be blocked by the administration of said antibody.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 5-9, 12-15 , 24, 25, 27 and 28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-4 of copending Application No. 09/674,462 in view of the abstract of Pawelec et al (Cell Immunol, 1994, Vol. 158, pp. 241-252)

The instant claims are obvious over the co-pending claims because it is taught by Pawelec et al that signal 2 is the co-stimulatory signal required by T-cells for ac and that delivery of signal 1 alon results in hyporesponsiveness. Thus the instant method claims encompass inducing hyporesponsiveness in T-cells by blocking the CD86 interaction with CD28 and the second signal.

This is a provisional obviousness-type double patenting rejection.

All other rejections and objections as set forth in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
12/27/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER